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METHODS FOR SAMPLING AND ANALYSIS OF BREATH

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16. ABSTRACT

This research program surveyed and evaluated the methods and procedures used to identify and quantitate chemical constituents in human breath. Methods have been evaluated to determine their ease and rapidity, as well as cost, accuracy, and precision. During this evaluation, a second goal was to determine the feasibility of correlating a preferred method with easily identifiable chemical and physical characteristics of the analyte. To accomplish these goals, an extensive literature review was performed. The information retrieved was summarized and classified by sampling and analysis methodology. The sampling methods found include apnea collection, breathing value, cryogenic trapping, Tenax cartridge and cascade impactors. Analytical methods found are gas chromatography, mass spectroscopy and PIXE.

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FOREWORD

The Exposure Assessment Group (EAG) of EPA's Office of Health and Environmental Assessment, Office of Research and Development, has three main functions: (1) to conduct exposure assessments; (2) to review assessments and related documents; (3) to develop guidelines for Agency exposure assessments. The activities performed under each of these functions are supported by and respond to the needs of the various EPA program offices. In relation to the third function, EAG sponsors projects which develop or refine data and procedures or techniques used in exposure assessments. This report is the product of one of those projects, and was done for the Office of Solid Waste and Emergency Response.

The current project was initiated to provide an evaluation of the analytical methods and procedures currently used to identify and quantify chemical constituents in human breath. The emphasis in this report is placed on specific preparation methods used for breath analysis. These methods have been evaluated with regard to their ease and rapidity, as well as cost, complexity, specialized equipment required, accuracy and precision. The results of this work constitute basic guidance for the analysis of chemical compounds in breath; the Exposure Assessment Group eventually hopes to provide more detailed guidance on biomonitoring.

James W. Falco
Director
Exposure Assessment Group

ABSTRACT

This research program surveyed and evaluated the methods and procedures used to identify and quantitate chemical constituents in human breath. Methods have been evaluated to determine their ease and rapidity, as well as cost, accuracy, and precision. During this evaluation, a second goal was to determine the feasibility of correlating a preferred method with easily identifiable chemical and physical characteristics of the analyte.

To accomplish these goals, an extensive literature review was performed. The information retrieved was summarized and classified by sampling and analysis methodology. The sampling methods which were found include apnea collection, breathing value, cryogenic trapping, Tenax cartridge and cascade impactors. Analytical methods found were gas chromatography, mass spectroscopy and PIXE.

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ABBREVIATIONS AND SYMBOLS

ASV	Anodic Stripping Voltammetry
AAS	Atomic Absorption Spectroscopy
CV	Coefficient of Variance
COL	Colorimetry
CV_{-2}	Cyclic Voltammetry
cm	Centimeter Square
dL	Deciliter
°C	Degrees Centrigrade
EC	Electrochemical Methods
ES	Emission Spectroscopy
eV	Electron Volts
EDXRF	Energy Dispersive X-Ray Fluorescence
γ	Gamma Rays
GC	Gas Chromatography
g	Gram
HPLC	High Performance Liquid Chromatography
HCL	Hollow Cathode Lamp
ICAP	Inductively Coupled Argon Plasma
IR	Infrared
KeV	Kilo Electron Volt
LOD	Limit of Detection
L	Liter
MS	Mass Spectrometry
mL	Milliliter
m/e	Mass-to-Charge Ratio
MeV	Mega Electron Volts
mg	Milligram
μL	Microliters
μmol/L	Micro mol per liter
μg	Microgram
mM	Millimolar
NAA	Neutron Activation Analysis
NBS	National Bureau of Standards
ng	Nanogram
nm	Nanometers
Φ	Neutron Flux
NMR	Nuclear Magnetic Resonance
PIXE	Proton Induced X-Ray Emission
ppb	Parts Per Billion
pg	Picogram
ppm	Parts Per Million
RLD	Reciprocal Linear Dispersion
RSD	Relative Standard Deviation
SRM	Standard Reference Material
sec	Second
TLC	Thin Layer Liquid Chromatography
t	Time
UV	Ultraviolet

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SECTION 1
INTRODUCTION

The purpose of this research program was to survey and evaluate the methods and procedures used to identify and quantitate chemical constituents in human breath. Methods have been evaluated to determine their ease and rapidity, as well as cost, accuracy, and precision. During this evaluation, a second goal was to determine the feasibility of correlating a preferred method for breath analysis with easily identifiable chemical and physical characteristics of the analyte.

The literature search was restricted to lists of chemicals of current interest to the U.S. Environmental Protection Agency and initially to references cited in "Chemicals Identified in Human Biological Media, A Data Base" (1). In a followup effort, the open literature was searched using the Chemical Abstract Data Base.

The original list of target chemicals to be included in this review was compiled from a set of documents (2-5) received from the EPA Technical Project Monitor. The documents contained lists of compounds of interest to the EPA. The chemicals from these documents were then crossed referenced with the compounds listed in "Chemicals Identified in Human Biological Media, A Data Base" (1) and the Chemical Abstract Data Base.

A total of 67 chemicals (58 organics, 9 elements) were identified as having been determined in human breath. Only three analytical methods, gas chromatography (GC), mass spectrometry (MS) and proton-induced x-ray emission (PIXE), were cited as having been applied to breath analysis. Since the analytical methods themselves have been extensively reviewed in a companion document (6) considering six other matrices, only the specific preparation methods used for breath analysis will be discussed in this document. A complete list of the chemicals included in the search is included in the companion document.

SECTION 2

SUMMARY AND CONCLUSIONS

Several combinations of sampling, concentration and analysis methods were cited in the reviewed literature for the identification and quantitation of target compounds in human breath. This information is summarized in Table 2-1. A brief noncritical review of the advantages and disadvantages of each method follows.

In 1977 an international workshop on "The Use of Biological Specimens for the Assessment of Human Exposure to Environmental Pollutants" (30) summarized the data on the location or compartmentalization of xenobiotics and/or their metabolites in various biological matrices including breath. They concluded breath is not useful to evaluate exposure to arsenic, beryllium, cadmium, chromium, fluorine, lead, mercury, molybdenum, manganese, nickel, vanadium, zinc, copper, cobalt, platinum, palladium, tin, methyl mercury, DDT, phenoxy herbicides, pentachlorophenol, PCB, PBB, PCN, tetrachloro-dibenzo-p-dioxins, benzofuran, azobenzene, polycyclic hydrocarbons, amino and nitro derivatives, organophosphorus esters, cyanides, nitriles, mycotoxins, antibiotics, and hormonal substances. They concluded breath levels correlate with body burden in the cases of chlorinated solvents, plastic monomers, fluorinated propellants, nonsubstituted aliphatic and aromatic volatile hydrocarbons, alcohols, ethers, ketones, and carbon monoxide. It was also concluded selenium breath levels could possibly be useful as an indicator specimen, but further research was required to confirm selenium.

APNEA DIRECT INJECTION/GAS CHROMATOGRAPHY

The apnea sampling method combined with direct injection of the expired air into a gas chromatograph is an extremely simple and fast method which requires no specialized equipment. Since no concentration is achieved, however, the limit of detection is relatively high for this method.

TABLE 2-1. COMPOUNDS IDENTIFIED IN BREATH

Compound	CAS[a] No.	Method	Reference No.
Nitrogen Containing			
N,N-dimethyl formamide	68-12-2	apnea direct injection/GC-FID[b]	13
Alcohols			
Methanol	67-56-1	breathing valve/direct injection/GC-MS[c]	14
		breathing valve/adsorbent conc./GC-MS	14,16
		cryogenic trapping/GC-FID-ECD[d]-MS	18
n-butyl alcohol	71-36-3	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
iso-butyl alcohol	78-83-1	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
Aldehydes			
acetaldehyde	75-07-0	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
Carboxylic Acid Esters			
ethyl acetate	141-78-6	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
Nitro Compounds			
2-nitrotoluene	88-72-2	breathing valve/adsorbent conc./GC-MS	16
2-nitropropane	89-46-9	breathing valve/adsorbent conc./GC-MS	16
Ketones			
methyl ethyl ketone	78-93-3	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
methyl isobutyl ketone	108-10-1	breathing valve/adsorbent conc./GC-MS	16

(continued)

TABLE 2-1. (Cont'd.)

Compound	CAS No.	Method	Reference No.
Sulfur Compounds			
dimethyl disulfide	624-92-0	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
Ethers			
ethyl ether	60-29-7	breathing valve/adsorbent conc./GC-MS	16
p-dioxane	123-91-1	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
furan	110-00-9	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
Nitriles			
acetonitrile	75-05-8	breathing valve/adsorbent conc./GC-MS	16
Halogenated Aliphatics			
carbon tetrachloride	56-23-5	breathing valve/adsorbent conc./GC-MS	16
		Tenax/GC/MS	29
dichlorodifluoromethane	75-71-8	cryogenic trapping/GC-FID-ECD-MS	18
		Tenax/GC/MS	29
trichlorofluoromethane	75-69-4	cryogenic trapping/GC-FID-ECD-MS	18
chloroform	67-66-3	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
		Tenax/GC/MS	28
dichloromethane	75-09-2	apnea/collection/direct injection/GC-FID	10
		cryogenic trapping/GC-FID-ECD-MS	18
tetrachloroethylene	127-18-4	apnea direct injection/GC-FID	7
		breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
		Tenax GC/MS	29
trichloroethylene	79-01-6	breathing valve/direct injection/GC-FID	16
		cryogenic trapping/GC-FID-ECD-MS	18
		Tenax/GC/MS	29

(continued)

TABLE 2-1. (Cont'd.)

Compound	CAS[a] No.	Method	Reference No.
Halogenated Aliphatics (cont'd.)			
1,1,1-trichlorotrifluoroethane	354-58-5	cryogenic trapping/GC-FID-ECD-MS	18
vinylidene chloride	75-35-4	cryogenic trapping/GC-FID-ECD-MS	18
vinyl chloride	75-01-4	breathing valve/adsorbent conc./GC	17[e]
		cryogenic trapping/GC-FID-ECD-MS	18
1,1,1-trichloroethane	71-55-6	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
		Tenax/GC/MS	29
1,1-dichloroethane	75-34-3	cryogenic trapping/GC-FID-ECD-MS	18
		Tenax/GC/MS	29
dichloroethylene	75-35-4	breathing valve/adsorbent conc./GC-MS	16
1,2-dichloroethane	107-06-2	Tenax/GC/MS	29
carbon tetrachloride	56-23-5	Tenax/GC/MS	29
trichloroethylene	79-01-6	Tenax/GC/MS	29
tetrachloroethylene	127-18-4	Tenax/GC/MS	29
1,3-hexachlorobutadiene	87-68-3	Tenax/GC/MS	29
bromoform		Tenax/GC/MS	29
bromodichloromethane		Tenax/GC/MS	29
dibromochloromethane		Tenax/GC/MS	29
dibromochloropropane		Tenax/GC/MS	29
Halogenated Aromatics			
o-dichlorobenzene	95-50-1	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18[f]
		Tenax/GC/MS	29
m-dichlorobenzene	541-73-1	cryogenic trapping/GC-FID-ECD-MS	29
		Tenax/GC/MS	28

(continued)

TABLE 2-1. (Cont'd.)

Compound	CAS[a] No.	Method	Reference No.
Halogenated Aromatics (continued)			
p-dichlorobenzene	106-46-1	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18[f]
		Tenax/GC/MS	28,29
chlorobenzene	108-90-7	cryogenic trapping/GC-FID-ECD-MS	18
		Tenax/GC/MS	28,29
trichlorobenzene isomers	8	Tenax/GC/MS	28
tetrachlorobenzene isomers	8	Tenax/GC/MS	28
pentachlorobenzene	608-93-5	Tenax/GC/MS	28
chlorotoluene isomers	8	Tenax/GC/MS	28
dichlorotoluene isomers	8	Tenax/GC/MS	28
bromotoluene isomers	8	Tenax/GC/MS	28
chloronaphthalene isomers	8	Tenax/GC/MS	28
chlorobenzotrifluoride isomers	8	Tenax/GC/MS	28
Hydrocarbons			
ethyl acetylene	107-00-6	cryogenic trapping/GC-FID-ECD-MS	18
benzene	71-43-2	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
		Tenax/GC/MS	29
cyclohexane	110-82-7	breathing valve/adsorbent conc./GC-MS	16
n-hexane	110-54-3	apnea/direct injection/GC-FID	12
		breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18

(continued)

TABLE 2-1. (Cont'd.)

Compound	CAS[a] No.	Method	Reference No.
Hydrocarbons (cont'd.)			
toluene	108-88-3	apnea/direct injection/GC-FID	11
		breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
p-xylene	106-42-3	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
		Tenax GC/MS	29
m-xylene	108-38-3	breathing valve/adsorbent conc./GC-MS	16
		Tenax GC/MS	29
ethyl benzene	100-41-4	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
		Tenax GC/MS	29
p-cumene	98-82-8	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
mesitylene	108-67-8	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
naphthalene	91-20-3	breathing valve/adsorbent conc./GC-MS	16
		cryogenic trapping/GC-FID-ECD-MS	18
1,1-biphenyl	92-52-4	breathing valve/adsorbent conc./GC-MS	16
Metals			
calcium	7440-70-2	cascade impactors/PIXE	26,27
chromium	7440-47-3	cascade impactors/PIXE	26
lead	7439-92-1	cascade impactors/PIXE	26,27
manganese	7439-96-5	cascade impactors/PIXE	26

(continued)

TABLE 2-1. (Cont'd.)

Compound	CAS[a] No.	Method	Reference No.
Metals (cont'd.)			
nickel	7440-02-0	cascade impactors/PIXE	26
strontium	7440-24-6	cascade impactors/PIXE	26
titanium	7440-32-6	cascade impactors/PIXE	26
vanadium	7440-62-2	cascade impactors/PIXE	26
zinc	7440-66-6	cascade impactors/PIXE	26

[a]CAS = Chemical Abstract Service.

[b]FID = Flame Ionization Detector.

[c]MS = Mass Spectrometry.

[d]ECD = Electron Capture Detector.

[e]Detector not specified in reference 10.

[f]Isomer not specified in reference 11.

[g]Multiple CAS number.

BREATHING VALVE/DIRECT INJECTION/GAS CHROMATOGRAPHY

This method, like the apnea/direct injection/GC method, is simple and fast. A breathing valve, air tank, and sample collection bag are required making it slightly more complicated than the apnea method. Again, the sample is not concentrated before injection into the gas chromatograph, resulting in relatively high limits of detection. Because very little sample manipulation is performed, recoveries are high, however, specific numbers were not found in the literature reviewed.

BREATHING VALVE/ADSORBENT CONCENTRATION/GAS CHROMATOGRAPHY

This method is slow, complicated and expensive compared to the direct injection techniques. The concentration achieved, however, results in very low detection limits (as low as 1 part per trillion). This allows a much larger number of trace components to be identified and quantitated, but also leads to more problems with background interferences. Some reported recoveries are high, better than 95%, with coefficients of variation of 3-6%.

CRYOGENIC TRAPPING/GAS CHROMATOGRAPHY

This method concentrates the compounds of interest without concentrating the oxygen and nitrogen matrix due to the concurrent and continuous cryogenic sampling. The extended sampling period (60 minutes) results in the equivalent of sub-ppb detection limits, although interferences from the supply air increases the limit of detection for those compounds present in both the supply air and the breath sample. The cryogenic data must be converted to the amount of compound produced per hour before the data is at all meaningful. The cryogenic trapping method is sensitive, but also complicated, time-consuming, and requires a specialized cryogenic trapping system. No recovery data is available for this method.

TENAX GC CARTRIDGE/GC/MASS SPECTROMETRY

This method concentrates the compounds of interest by directly adsorbing the breath or breath collected in a Tedlar bag onto a Tenax cartridge. The Tenax cartridge is later thermally desorbed and injected into a GC/mass spectrometer. This method has excellent sensitivity, but it is costly and requires elaborate equipment. The percent recovery for laboratory samples ranges from 77 to 110 percent.

CASCADE IMPACTOR SAMPLING/PHOTON INDUCED X-RAY EMISSION (PIXE) ANALYSIS

This is a sensitive, but very complicated, method for elemental analysis of breath. Exhaled air (4-6 L) is concentrated for PIXE analysis, using a cascade impactor which results in detection limits at the nanogram level. Sample collection efficiency is high (85-99%) which should lead to high recoveries. The disadvantage of this technique is that a large amount of specialized and expensive equipment is required, including cascade impactors, a computer for spectral analysis and a Van de Graff accelerator for PIXE analysis.

SECTION 3

RECOMMENDATIONS

The goal of this research program was to evaluate methodologies for analyzing chemicals of interest to EPA in human breath. Based on the extensive review performed for this program, we have found some simple and expected correlations between the chemical and physical characteristics of the compounds of interest and the method by which they are analyzed.

1. Most organic compounds can be determined by using a GC or GC/MS analytical technique.
2. With the exception of lithium and beryllium, most metals can be determined by PIXE analytical technique.
3. Adsorption onto Tenax cartridges is the most widely used sampling method to preconcentrate organic compounds, including hydrocarbons, chlorinated hydrocarbons, alcohols, ketones, nitrogen-containing compounds and others.

SECTION 4

PREPARATION METHODS FOR ORGANIC ANALYSIS

Preparation methods for organic analysis of breath samples usually involve collection of expired air from the subject and, if necessary, manipulation of the sample (concentration, etc.) for analysis by gas chromatography (GC).

APNEA/DIRECT INJECTION/GC

Principle of the Technique

In the apnea method, the subject inspires deeply, holds his breath for a period of 5-30 sec, and then forcibly expires through a sampling tube which is open at both ends. Just before the expiration is finished, the tube is closed at both ends, retaining a portion of the expiratory reserve volume in the tube. The collection tubes are equipped with perforated screw caps with a rubber disk and Teflon membrane, permitting small volumes of air (<25 µl) to be taken by syringe for gas chromatographic analysis without opening the tube.

Chemicals Determined

A wide variety of compounds have reportedly been sampled using this technique, including tetrachloroethylene (7), trichloroethylene (8), dichloromethane (9,10), toluene (11), hexane (12), and N,N-dimethylformamide (13).

Method Interferences

No data available.

Concentration Factor/Limit of Detection

No concentration is achieved using this method. Detection limits for direct injection depend upon compound type, GC detector, and volume of sample injected. A limit of detection of 0.1 mg/m^3 (14 ppb) was reported for tetrachloroethylene using flame ionization detection (7).

Recovery Data/Quantitation Method

No data available.

Method Precision

A coefficient of variation of 8% for the analysis of tetrachloroethylene at concentrations above 1 mg/m^3 has been reported (7).

Simplicity, Cost and Sample Throughput

The apnea/direct injection method is extremely simple and rapid, and does not require specialized equipment. The rate limiting step is the gas chromatographic analysis. Depending upon GC conditions, 2 to 3 samples can be analyzed per hour.

BREATHING VALVE/DIRECT INJECTION/GC

Principle of the Technique--

Exhaled air samples are collected in a Mylar® (14) or Tedlar® (15) bag using a breathing valve during one minute of normal breathing. The exhaled air is analyzed by injecting 25-1000 µl (15) or 5 mL (14) directly onto the gas chromatograph.

Chemicals Determined

Trichloroethylene (15) and methanol (14) are the only target compounds which have reportedly been analyzed by this method.

Method Interferences

No data available.

Concentration Factor/Limit of Detection

No concentration is achieved by this method. A detection limit of 0.9 µg/liter (.16 ppm) was reported for trichloroethylene using flame ionization detection (15).

Recovery Data/Quantitation Method

Losses for this method should be almost entirely due to adsorption of the compounds of interest to the sampling bags. The Mylar® bags were conditioned twice with breath before the actual sample was collected in an attempt to prevent such adsorption. Overall recovery of ~90% is reported (14).

Method Precision

A coefficient of variation of 7% has been reported for the analysis of trichloroethylene using flame ionization detection (15).

Simplicity, Cost and Sample Throughput

This method, like the apnea/direct injection method, is simple and rapid. The only specialized equipment required is the air tank, breathing valve, and sample collection bag. It has been reported that the entire procedure, including both sampling and analysis, can be performed in 15 minutes (14).

BREATHING VALVE/ADSORBENT CONCENTRATION/GC

Principle of the Technique

A breathing valve is used to collect exhaled air either in bags (14,16) or onto charcoal tubes (17). Samples collected in bags are concentrated by passing the exhaled air through adsorbent tubes containing Tenax GC (16) or activated charcoal (14). The adsorbent tubes are then connected to the injection port of the gas chromatograph and the compounds of interest are thermally desorbed onto the GC.

A number of studies focused on determining volatile organics in breath as a clinical diagnostic technique. They have used direct injection of the gas sample in a gas chromatograph after cyrogenic trapping or adsorption onto Tenax GC. Table 4-1 shows a summary of these studies.

Chemicals Determined

Target compounds which have reportedly been analyzed using the breathing valve/adsorbent concentration technique are listed in Table 4-2.

Method Interferences

The results of twenty measurements of the background constituents of the Teflon bag/Tenax GC system (16) are summarized in Table 4-3. These background checks were performed over a period of 18 months and show the presence of 12 low frequency and low concentration artifacts. Acetone, isoprene, and butane were observed at higher concentrations more frequently.

Concentration Factor/Limit of Detection

Concentration factors depend upon sample size and GC detector. Samples ranged from 1 liter of exhaled air passed through charcoal and then onto the GC (14) to 20 liters of exhaled air concentrated on Tenax GC and then desorbed into the GC/MS system (15). A limit of detection of 0.3 mg/m^3 (0.12 ppm) has been reported for vinyl chloride (17); but the detection method was not specified. While no limit of detection is specifically reported for the

TABLE 4-1. BREATH ANALYSIS FOR CLINICAL DIAGNOSIS

Compound in Breath	Disease or Altered Metabolism	Reference
Hydrogen	Carbohydrate malabsorption syndrome, intestinal overgrowth syndrome	19
Methane	Cancer of large bowel	20
Pentane	Increased lipid peroxidation caused by alcoholic cirrhosis	21
Ethane, Pentane; also lesser amounts of ethene, propane, butane	Chemically-induced lipid peroxidation in rats	22
Dimethyl sulfide	Cirrhosis	23
Short-chain fatty acids	Cirrhosis, Jamaican vomiting sickness	19
Dimethylamine, trimethylamine	End-stage renal disease (uremic)	24
Pyridine, 2-, 3-, and 4-methyl pyridine (saliva volatiles)	Moderate to severe periodontitis	25
Acetone	Diabetic ketoacidosis, starvation	19
Acetaldehyde, alcohols	Alcoholic intoxication	19

TABLE 4-2. TARGET COMPOUNDS ANALYZED BY BREATHING VALVE/ADSORBENT CONCENTRATION

Compound	Adsorbent	Reference No.
methanol	Tenax	16
methanol	Charcoal	14
n-butyl alcohol	Tenax	16
iso-butyl alcohol	Tenax	16
acetaldehyde	Tenax	16
ethyl acetate	Tenax	16
2-nitrotoluene	Tenax	16
2-nitropropane	Tenax	16
methyl ethyl ketone	Tenax	16
methyl isobutyl ketone	Tenax	16
dimethyldisulfide	Tenax	16
ethyl ether	Tenax	16
p-dioxane	Tenax	16
furan	Tenax	16
acetonitrile	Tenax	16
carbon tetrachloride	Tenax	16
chloroform	Tenax	16
tetrachloroethylene	Tenax	16
1,1,1-trichloroethane	Tenax	16
dichloroethylene	Tenax	16
o-dichlorobenzene	Tenax	16
p-dichlorobenzene	Tenax	16
benzene	Tenax	16
cyclohexane	Tenax	16
n-hexane	Tenax	16
toluene	Tenax	16
p-xylene	Tenax	16
m-xylene	Tenax	16
ethyl benzene	Tenax	16
p-cumene	Tenax	16
mesitylene	Tenax	16
naphthalene	Tenax	16
1,1-biphenyl	Tenax	16
vinyl chloride	Charcoal	17

TABLE 4-3. BACKGROUND OF EXPIRED AIR COLLECTION SYSTEM (TEFLON BAG/TENAX GC)[a]

Compound	Concentration Range (ng/liter)	% Occurrence
acetone	0.4-1.5	100
isoprene	0.5-0.9	100
butane	0.2-0.6	44.4
acetaldehyde	0.02-0.08	22.2
methanol	0.02-0.04	16.7
ethanol	0.06-0.09	16.7
chloroform	0.1-0.2	16.7
toluene	0.2-0.5	11.1
n-butyl alcohol	0.02-0.08	11.1
3-methyl-1-hexene	0.03-0.09	11.1
2,3,5-trimethylhexane	0.01-0.04	11.1
trimethylbenzene	0.09	5.6
o-nitrotoluene	0.001	5.6
1,1,1-trichloropropane	0.09	5.6
naphthalene	0.05-0.09	5.6

[a]From Reference No. 16

Teflon bag/Tenax GC/MS system (16), it appears to be highly sensitive in that quantities as low as 0.001 ng/liter (ppt range) are reported.

Recovery Data/Quantitation Method

Recoveries of 99.3% for acetone at 152 ng/liter and 97.1% for methylfuran at 0.35 ng/liter were reported using high resolution gas chromatography/mass spectrometry with automatic data acquisition and processing with the Teflon bag/Tenax technique (16).

Method Precision

Coefficients of variation of 3.9% for acetone and 5.9% for methylfuran are reported (16).

Simplicity, Cost and Sample Throughput

These techniques are relatively expensive, complicated and slow. Specialized equipment is required for sampling, concentration, and connection of the adsorbent tube to the injection port of the gas chromatograph. In the case of the Tenax GC technique (16), a means of desorbing the Tenax and transferring the compounds of interest onto the GC column is required.

CRYOGENIC TRAPPING/GC

Principle of the Technique

A multistage cryogenic sampling system has been described (18) for direct collection of human expired air samples over an extended time period. The system is designed to concentrate organic contaminants without concentrating the oxygen and nitrogen matrix. The experimental hardware includes the air supply, a one-way breathing valve, two water traps, two cryogenic sampling systems, and a dry gas meter for volumetric measurement. Cryogenic sampling of both the supply air and the expired air was done concurrently and continuously throughout the 60 minute sampling period. The cryogenic samples were analyzed by gas chromatography with the effluent split three ways to provide samples for flame ionization and electron capture detection, and a sample for mass spectrometer fragmentation analysis.

Chemicals Determined

The target compounds reportedly analyzed using this technique are listed in Table 4-4.

TABLE 4-4. TARGET COMPOUNDS ANALYZED USING CRYOGENIC TRAPPING TECHNIQUE[a]

methanol	vinyl chloride
n-butyl alcohol	1,1,1-trichloroethane
iso-butyl alcohol	1,1-dichloroethane
acetaldehyde	o-dichlorobenzene[b]
ethyl acetate	m-dichlorobenzene[b]
methyl ethyl ketone	p-dichlorobenzene[b]
dimethyl disulfide	chlorobenzene
p-dioxane	ethyl acetate
furan	benzene
dichlorodifluoromethane	n-hexane
trichlorofluoromethane	toluene
chloroform	p-xylene
dichloromethane	ethyl benzene
tetrachloroethylene	p-cumene
trichloroethylene	mesitylene
1,1,1-trichlorotrifluoroethane	naphthalene
vinylidene chloride	

[a] From Reference No. 11

[b] Not specific isomer.

Method Interferences

The only method interferences reported are those compounds of interest which are present in the supply air (18). These compounds are listed in Table 4-5.

Concentration Factor/Limit of Detection

This method concentrates the compounds of interest without concentrating the oxygen and nitrogen matrix due to the concurrent and continuous cryogenic sampling. This allows the equivalent of sub-ppb detection levels (18). Using benzene as an example, the reported value of 0.12 μg/hr is equivalent to a direct sample of 0.1 ppb.

Recovery Data/Quantitation Method

No recovery data is available. Compound quantitation was done by digital integration of the chromatographic peaks. Data was converted to amount of compound collected in μg/hr using the following formula (18):

$$Y_i = W_i \times \frac{(60)}{t} \times \frac{(V_1 + V_2)}{V_2}$$

where

Y_i = production of compound i, in μg/hr

W_i = collected of compound i in cryotrap sample, μg

V_1 = volume gas diverted through cryotrap, liters

V_2 = volume gas measured on dry gas meter, liters

t = time of trapping, minutes

Method Precision

No data available.

Simplicity, Cost, and Sample Throughput

This method is complicated, time-consuming, and requires a rather sophisticated specialized cryogenic sampling system.

TABLE 4-5. TARGET COMPOUNDS PRESENT IN SUPPLY AIR[a]

Compound	Concentration (μg/liter)[b]
chloroform	0.004
1,1,1-trichloroethane	0.036
trichloroethylene	0.001
vinylidene chloride	0.001
hexane	0.006
ethyl acetylene	0.003
benzene	0.035
toluene	0.022
furan	0.022
methanol	0.016
n-butyl alcohol	0.004
iso-butyl alcohol	0.008
methyl ethyl ketone	0.017
methyl isobutyl ketone	0.043
acetaldehyde	0.007
ethyl acetate	0.006
dimethyl disulfide	0.020

[a]From Reference No. 18

[b]Average of 6 cylinders.

TENAX GC CARTRIDGE/GC/MASS SPECTROSCOPY

Principle of the Technique

Breath samples are collected by means of a spirometer. The subject breaths humidifed ultrapure air. The exhaled air is pumped through a Tenax GC cartridge to collect organic compounds. The sampling cartridges are prepared by packing an 8 cm x 1.5 cm I.D. glass tube with 6.0 cm of 35/60 mesh Tenax GC, using glass wool in the ends to provide support. Prior to packing in cartridges, the Tenax is extracted in a Soxhlet extractor for a minimum of 24 hours with methanol and then pentane prior to preparation of cartridge samplers. The cartridges are desorbed and analyzed by a thermal desorption technique using an inlet manifold system (28).

Chemicals Determined

A number of volatile organics have been analyzed using this technique. Table 4-6 shows the reported compounds (28,29).

Method Interference

Unexposed Tenax cartridges have been analyzed during field studies to estimate contamination and method interferences. Results in Table 4-7 show levels of target volatiles found on Tenax cartridges taken to the field (field blanks) and those stored in the laboratory (lab blanks). Additional studies have shown minimal contamination resulting from collecting the air sample in a Tedlar bag. Studies with the Tedlar bags have also demonstrated little diffusion of organics from ambient air through the bags (29).

Concentration Factor/Limit of Detection

Concentration factors depend upon sample size and mass response.

Method detection limits for some volatile organics are listed in Table 4-6 assuming a 20 L sample size.

Recovery Data/Quantitation Method

Recoveries of volatile organics from Tenax GC measured using spiked controls are given in Table 4-8. Table 4-9 shows recoveries of selected volatiles from the Tedlar bag. Quantitation is performed by generating a response factor for a known quantity of each standard volatile to an external

TABLE 4-6. METHOD LIMITS OF DETECTION USING A 20 L BREATH SAMPLE

Compound	Breath Concentration (ng/L)
Vinylidene chloride	0.40
Chloroform	0.30
1,2-Dichloroethane	0.30
1,1,1-Trichloroethane	0.35
Carbon tetrachloride	0.45
Trichloroethylene	0.70
Bromodichloromethane	0.50
Chlorodibromomethane	0.50
Tetrachloroethylene	0.45
Chlorobenzene	0.20
Bromoform	0.50
Dibromochloropropane	0.85
p-Dichlorobenzene	0.20
o-Dichlorobenzene	0.20
Benzene	0.15
Ethylbenzene	0.10
Styrene	0.20
o-Xylene	0.15
p-Xylene	0.15
1,1-Dichloroethane	~0.30
1,3-Hexachlorobutadiene	ND[a]
Trichlorobenzenes	ND
Tetrachlorobenzene isomer(s)	ND
Pentachlorobenzene	ND
Chlorotoluene isomer(s)	ND
Dichlorotoluene isomer(s)	ND
Bromotoluene isomer(s)	ND
Chloronaphthalene isomer(s)	ND
Chlorobenzotrifluoride	ND

[a]No data available.

TABLE 4-7. BLANK DATA FOR BREATH VOLATILES

Compound	ng/cartridge ± S.D.	
	Field[a]	Lab[b]
Vinylidene chloride	1 ± 2	<1
Chloroform	22 ± 20	8 ± 6
1,2-Dichloroethane	<1	<1
1,1,1-Trichloroethane	33 ± 21	14 ± 17
Benzene	97 ± 64	41 ± 26
Carbon tetrachloride	2 ± 3	15 ± 42
Trichloroethylene	3 ± 5	1 ± 2
Bromodichloromethane	ND	ND
Dibromochloromethane	ND	ND
Tetrachloroethylene	11 ± 10	2 ± 4
Chlorobenzene	1 ± 3	2 ± 3
Bromoform	ND	ND
Dibromochloropropane	<1	ND
Styrene	2 ± 3	2 ± 3
p-Dichlorobenzene	3 ± 7	1 ± 1
Ethylbenzene	12 ± 13	5 ± 10
o-Xylene	8 ± 9	3 ± 5
p-Xylene	22 ± 21	7 ± 11
o-Dichlorobenzene	1 ± 2	1 ± 1

[a] N = 76.

[b] N = 79.

TABLE 4-8. CONTROL DATA FOR AIR AND BREATH VOLATILES

Compound	% Recovery ± S.D.	
	Field[a]	Lab[b]
Vinylidene chloride	85 ± 23	110 ± 33
Chloroform	89 ± 22	90 ± 39
1,2-Dichloroethane	100 ± 15	106 ± 31
1,1,1-Trichloroethane	87 ± 19	94 ± 28
Benzene	86 ± 22	90 ± 26
Carbon tetrachloride	80 ± 20	93 ± 24
Trichloroethylene	95 ± 12	99 ± 24
Bromodichloromethane	96 ± 19	98 ± 11
Dibromochloromethane	95 ± 17	93 ± 13
Tetrachloroethylene	108 ± 18	109 ± 29
Chlorobenzene	110 ± 24	109 ± 32
Bromoform	96 ± 19	92 ± 15
Dibromochloropropane	96 ± 17	77 ± 24
Styrene	104 ± 14	92 ± 15
p-Dichlorobenzene	101 ± 11	87 ± 13
Ethylbenzene	95 ± 14	95 ± 18
o-Xylene	100 ± 13	88 ± 19
p-Xylene	100 ± 14	91 ± 18
o-Dichlorobenzene	96 ± 13	85 ± 15

[a] N = 110.
[b] N = 91.

standard. One reported method used perfluorotoluene and perfluorobenzene as external standard. Response factors were generated using spiked Tenax cartridges (29).

Method Precision and Accuracy

Accuracy and precision may be estimated from Table 4-8. Analysis of duplicate samples generally show reproducibility to be ±25%.

Simplicity, Cost and Sample Throughput

This technique is relatively expensive since a GC/MS is needed. Sample throughput is not high due to calibration and quality control requirements.

METHOD/ANALYTE CORRELATION PARAMETERS

All of the methods for organic analyses are applicable to volatile compounds; i.e., those with boiling points <150 to 200°C. The least volatile compound identified was 1,1-biphenyl (bp 255°C) using a breathing valve/adsorbent concentration/GC-MS; however, recoveries were not given and cannot be assumed as quantitative. For the direct injection methods, condensation onto container surfaces should limit analysis of less volatile compounds. Efficient thermal desorption from sorbent tubes is a serious problem for less volatile compounds. Finally, some very volatile compounds (i.e., bp <50°C) and volatile polar compounds (such as methanol and ethanol) will not be retained by Tenax GC during concentration.

TABLE 4-9. RECOVERIES FROM TEDLAR BAG

Amount Spiked (ng)	Conditions Humidity	% Recovery ± Standard Deviation[a]		
		Benzene	Tetrachloroethylene	Chlorobenzene
100-200	100%	81 ± 0.7	212 ± 2.1	99 ± 0.7
300-600	100%	89 ± 2.1	112 ± 0.7	107 ± 1.4
100-200	0%	110 ± 12.0	114 ± 28[b]	95 ± 9[b]
150-300	0%	NT	108 ± 3.5	102 ± 3.5
5-10	100%	93 ± 15[c]	118 ± 16[c]	97 ± 14[c]

[a]Duplicate determinations.

[b]Average of four determinations.

[c]Average of seven determinations.

SECTION 5

PREPARATION METHODS FOR ELEMENTAL ANALYSIS

Preparation methods for elemental analysis of human breath involve collection of small aerosol deposits which are analyzed for principal elemental constituents using proton induced x-ray emission (PIXE).

CASCADE IMPACTOR SAMPLING

Principle of the Technique

Aerosol particles are sampled using 5 and 6 stage cascade impactors where each stage produces a single small aerosol deposit suitable for PIXE analysis (26,27). Ambient and exhaled airs are each sampled by a pair of impactors operating at flow rates of 12 L/min and 1 L/min giving resolution down to a 0.5- and 0.25-μm diameter, respectively, on the impaction stages. The 50% cutoff diameters for unit density spherical particles on the stages are 4, 2, 1, 0.5, and 0.25 μm for the first five stages and the sixth filter stage is for particles <0.25-μm diameter. The exhaled air samples are housed in an enclosure kept at about 40°C to avoid vapor condensation and a constant flow rate is maintained by the subject's inhaling through his nose and exhaling through his mouth into a plastic bag from which air is drawn into the impactor. As an additional refinement, a flowmeter is included between the subject and plastic bag to permit voluntary control of breathing frequency and tidal volume by observing flow rate during the experiment. Each cascade impactor is equipped with paraffin-coated polystyrene film impaction surfaces, supported by 25 mm diameter glass slides with a 0.4 μm Nucleopore backup fine particle filter. After sampling, these samples are removed from the impactor, separated from the glass support, and mounted on frames for proton irradiation.

Chemicals Analyzed (Elements Determined)

Calcium (26,27), lead (26,27), manganese (26), chromium (26), nickel (26), titanium (26), vanadium (26), zinc (26), and strontium (26) have reportedly been analyzed using the cascade impactors/PIXE technique.

Method Interferences

No data available.

Concentration Factor/Limit of Detection

Detection limits have been reported for several elements as reported in Table 5-1 (26). No specific information on concentration factor is reported, although the volume of air sampled ranges from 4-7 liters per sample (30).

Recovery Data/Quantitation Method

No recovery data is available, although filter efficiency of 85-99% is reported (26). Spectra are stored on magnetic tape and later resolved by computer programs so that a quantitative analysis may be made for each element in the sample (26).

Method Precision

No data available.

Simplicity, Cost and Sample Throughput

This method is complicated, expensive and requires a large number of specialized pieces of equipment, including the cascade impactors and a Van de Graaff accelerator for the PIXE analysis.

METHOD/ANALYTE CORRELATION PARAMETERS

From the limited data available, it appears that all metals which can be analyzed using PIXE are amenable to breath analysis using cascade impactor sampling.

TABLE 5-1. DETECTION LIMITS FOR ELEMENTS OF INTEREST USING CASCADE IMPACTOR/PIXE TECHNIQUE[a]

Element	Detection Limit (ng)
calcium	1.3
vanadium	0.9
titanium	0.6
chromium	0.2
manganese	1.7
nickel	1.0
zinc	1.4
lead	9.8
strontium	8.7

[a]From Reference No. 26

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